PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17.08.2005
Applicant's or agent's file reference: PAM-015-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003668	06.04.2004	10.04.2003

Applicant
PAMGENE B.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
PAM-015-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003668	06.04.2004	10.04.2003
International Patent Classification (IPC) or national classification and IPC		
B01J19/00, G01N33/551, G01N33/543		
Applicant		
PAMGENE B.V.		

1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.01.2005	17.08.2005
Name and mailing address of the International preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003668

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-26 as originally filed

Claims, Numbers

1-17 received on 21.01.2005 with letter of 22.12.2004

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reference is made to the following documents:

D1: WO 02/26376 A (SURMODICS INC) 4 April 2002 (2002-04-04)

D2: WO 99/02266 A (AKZO NOBEL NV ;DAMME HENDRIK SIBOLT VAN (NL); KREUWEL HERMANUS JOH) 21 January 1999 (1999-01-21)

1. The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and (see passages cited in the Search Report) discloses functionalized substrates, such as functionalized ceramic, functionalized silica or functionalize glass, in which functionalization means addition of organic modification to an inorganic surface, by known methods, to provide bonds with which the photoreactive groups can react (page 9, lines 8-14).

Under the heading "Photoreactive Groups on the Substrate Surface" (bridging pages 10 and 11) an example of this functionalization is given in the form of poly-l-lysine on glass, which is "generally bound to the surface via Silyl-OH groups" (which are the same silyl-OH groups normally found on silica). Then nucleic acid sequences can be printed on then, after which the surface is illuminated (i.e., subjected to electromagnetic irradiation) to cross-link the nucleic acids to the polymer (page 11, lines 9-21). It is used for performing probe-based assays.

On page 9, lines 19-25, the provision of three-dimensional surfaces using a support that is permeable (i.e., implicitly being porous and having through-going channels) to allow nucleic acids to migrate into the pores is described as giving a higher density of nucleic acids.

The subject-matter of the independent claims differs from this disclosure in that the channels are "oriented".

Therefore, these claims are novel over D1 (Article 33(1) and (2) PCT).

2.1 The problem to be solved cannot be regarded to be overcoming "the difficulties of polymer coating of inert porous metal oxide substrates" for two reasons:
a) the qualification "inert" does not appear in the claims. In addition many, if not all, oxides, such as alumina or silica, normally possess many OH groups on the surface, which

are reactive (often acidic, so that interaction with a basic compound would be easy) and can therefore hardly be considered as "inert". It is also mentioned in D1 that these OH-groups are responsible for the fixation of the poly-l-lysine.
b) the only relevant technical feature in the claims relating to the actual coating of the polymer is "bringing said substrate into contact with a solution comprising said polymer". Apart from being known from D1, this would not appear to overcome much difficulty but rather be a quite obvious step.

2.2 The objective problem to be solved must find its origin in the difference with D1. This difference lies in the channels being "oriented".

No surprising effects, resulting from this difference, could readily be identified in the application.

The objective problem to be solved should, thus, be considered as merely providing an alternative permeable metal oxide substrate, suitable for being coated by a polymer for immobilizing biomolecules.

D2 (see passages cited in the Search Report) describes metal oxide substrates with porous, through-going channels for immobilizing biomolecules (particularly electrochemically etched metal sheets are mentioned and more particularly aluminum oxide membranes). It describes a range of advantages associated with these substrates. There is no indication whatsoever in D2 that these substrates would be unsuitable for coating with a polymer.

When wishing to provide an alternative permeable metal oxide substrate, suitable for use in assays and kits, the skilled person would have encountered D2 and, considering the many advantages associated with it, would also have considered it as very suitable alternative substrate for those mentioned in D1.

2.3 Thus, none of the independent claims gives rise to an inventive step, contrary to the requirements of Article 33(3) PCT.

2.4 None of the dependent claims appears to be able to give rise to an inventive step

because their features are either already disclosed in D1 or D2, or would (in the absence of specific advantages) be known to be common replacements the skilled person would choose from as a matter of course when wishing to provide an alternative.

Re Item VIII

The independent claims are not in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art (document D1) being placed in the preamble (Rule 6.3(b)(I) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

Claims (Retyped)

1. A method for providing biomolecules on a porous metal oxide substrate having oriented through-going channels comprising the steps of:
   a) coating said porous metal oxide substrate with a polymer by bringing said substrate into contact with a solution comprising said polymer such that the polymer in said solution is able to form a coating on a surface of said substrate,
   b) deposing said biomolecules onto the porous metal oxide substrate obtained in step a) by bringing said biomolecules into contact with said substrate, and
   c) immobilizing said biomolecules onto the porous metal oxide substrate obtained in step a) by covalently binding said biomolecules to said substrate by means of electromagnetic irradiation.

2. A method according to claim 1, wherein said polymer is substantially adsorptively bound on the porous metal oxide substrate.

3. A method according to claim 1 or 2, wherein said polymer comprises multiple amide functional groups and/or multiple cationic functional groups.

4. A method according to any of claims 1 to 3, wherein said polymer is selected from the group comprising poly-aspartate, poly-glutamate, poly-cysteine, poly-serine, poly-methionine, poly-arginine, poly-histidine, poly-tryptophane, poly-alanine, poly-lysine, poly-leucine, poly-isoleucine, poly-tyrosine, poly-valine, poly-glycine, poly-proline, poly-phenylalanine, poly-threonine, polymers of other natural and non-natural amino acids and derivatives and mixtures thereof.

5. A method according to claim 4 wherein said polymer is poly-L-lysine.

6. A method according to any of claims 1 to 5, wherein said metal oxide substrate is an aluminium oxide substrate.

7. A method according to any of claims 1 to 6, wherein the biomolecules are immobilized on the substrate in spots, thereby forming an array of spots.

8. A method according to any of claims 1 to 7, wherein said biomolecules comprise the same or different biomolecules.

9. A method according to any of claims 1 to 8 wherein said biomolecules are selected from the group comprising oligonucleotides, polynucleotides, ribonucleotides, proteins, antibodies, antigens, peptides, oligo or poly saccharides, receptors, haptens, ligands, antibodies, antigens, peptides, oligo or poly saccharides, receptors, haptens and ligands, drugs, toxins and liposomes.

10. A porous metal oxide substrate having oriented through-going channels obtainable according to the method of any of claims 1 to 9, having a surface that is coated with a polymer, said porous metal oxide substrate having biomolecules immobilised thereon, wherein said biomolecules are immobilised on said substrate by covalent binding by means of electromagnetic irradiation.

11. A porous metal oxide substrate according to claim 10, wherein said porous metal oxide substrate is a porous aluminium oxide substrate.

12. A porous metal oxide substrate according to claim 10 or 11, wherein said porous metal oxide substrate has a surface that is coated with a polypeptide, and preferably with poly-L-lysine.

13. A kit or parts of a kit comprising a porous metal oxide substrate according to any of claims 10 to 12, further comprising a detection means for determining whether binding has occurred between biomolecules and an analyte.

14. A kit according to claim 13, wherein the detection means is a substance capable of binding to the analyte and being provided with a label.

15. A kit according to claim 14, wherein the label is capable of inducing a colour reaction and/or capable of bio-, chemi- or photoluminescence.

16. Method for performing probe-based assays, comprising the steps of:

contacting a sample comprising an analyte to a porous metal oxide substrate having oriented through-going channels and having biomolecules immobilised thereon according to any of Claims 10 to 12;

incubating said sample with said porous metal oxide substrate under conditions suitable for allowing binding of said analyte in said sample to said biomolecules immobilised on porous metal oxide said substrate; and

detecting the binding of said analyte in said sample to said biomolecule immobilised on said substrate.

17. Use of a metal oxide substrate according to any of Claims 10 to 12 for performing probe-based assays.